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## Infarct Size Reduction by Propranolol before and after Coronary Ligation in Dogs

MARGARET M. RASMUSSEN, M.D., PH.D., KEITH A. REIMER, M.D., PH.D.,

ROBERT A. KLONER, M.D., PH.D., AND ROBERT B. JENNINGS, M.D.

**SUMMARY** Coronary occlusion in the dog results in irreversible myocardial cell injury which develops first in subendocardial areas of severe ischemia and subsequently spreads into mid and subepicardial areas of moderate ischemia. The effect of propranolol on this progression of ischemic injury was evaluated. Three groups of dogs were studied: 1) untreated, 2) treated with propranolol before and throughout coronary ligation, and 3) treated with propranolol beginning three hours after ligation. Dogs were sacrificed 24 hours after coronary ligation and necrosis was quantitated from histologic sec-

tions of transmural slices through the posterior papillary muscle. Propranolol reduced infarct size by preventing necrosis in peripheral (subepicardial) areas of moderately ischemic myocardium. Pre-treatment with propranolol reduced necrosis from  $85 \pm 3\%$  (untreated) to  $52 \pm 4\%$  ( $P < 0.05$ ). Delayed propranolol therapy was about half as effective as pre-treatment and reduced necrosis to  $71 \pm 3\%$  ( $P < 0.05$ ). Propranolol also limited microvascular injury so that perfusion defects, detected with the dye thioflavin S, were smaller in treated dogs.

**MYOCARDIAL CELL DEATH** following acute coronary occlusion, develops first in severely ischemic subendocardial myocardium, and progressively spreads to involve areas of moderately ischemic mid- and subepicardial myocardium.<sup>1-4</sup> Many studies have supported the idea that this process can potentially be limited by early pharmacologic, mechanical or surgical intervention.<sup>5-7</sup>

Previous studies have demonstrated that a blockade with propranolol or practolol reduces epicardial or precordial ST segment elevation following experimental coronary occlusion or following myocardial infarction in man.<sup>8-10</sup> Histologic studies of necrosis following temporary coronary occlusions have provided direct demonstration that propranolol delays cell death in areas of severe ischemia.<sup>11-13</sup>

The present study was done to determine whether necrosis within the peripheral, moderately ischemic zone of infarcts produced by permanent coronary ligation in dogs could be

limited by propranolol. Infarct size was significantly reduced by propranolol therapy instituted prior to, and maintained throughout coronary occlusion. Intervention with propranolol three hours after coronary ligation was less effective but still produced a significant reduction in infarct size.

### Materials and Methods

Mongrel dogs of both sexes weighing 9-28 kg were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and ventilated with a Harvard (Model 1063) respirator. Aseptic surgical techniques were used. Lead II of the standard electrocardiogram (ECG) and peripheral blood pressure, via a catheter in the right femoral artery, attached to a Statham (P23AC) pressure transducer, were monitored on a Grass (Model 5) polygraph. The right saphenous vein was catheterized for propranolol or saline infusion and both catheters were kept open with dilute heparinized saline.

The chest was opened in the fourth left intercostal space, the pericardium was incised, and the circumflex coronary artery was isolated 1-2 cm from the aorta. Dogs in a pretreated group (group B) were given 5 mg/kg propranolol (intra-arterially) 10 min prior to coronary occlusion and an additional 1.0 mg/kg/hr in heparinized saline was infused intravenously at 0.7 cc/min beginning 30 min after occlusion

From the Departments of Pathology, Northwestern University Medical School, Chicago, Illinois, and Duke University Medical Center, Durham, North Carolina.

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Address for reprints: Keith A. Reimer, M.D., Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710.

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and continuing until sacrifice at 24 hours. An untreated group (group A) was given isotonic heparinized saline without propranolol at the same rate and the same routes as dogs in group B. A third group of dogs (group C) was given delayed propranolol therapy beginning with 5.0 mg/kg propranolol three hours after occlusion and followed 30 min later with an intravenous infusion at 1.0 or 2.0 mg/kg/hr until sacrifice.

Permanent occlusions were done by double ligation. Following placement of the first ligature, a catheter was placed in the artery for measurement of peripheral coronary pressure (PCP). The catheter was then removed and the second ligature placed. Incisions were closed and all animals were allowed to recover from anesthesia for 24 hours. Approximately 24 hours after occlusion, dogs were re-anesthetized. The fluorescent dye, thioflavin S (TS) (1.0 cc/kg of a 4% solution) was injected intravenously to demonstrate areas with collateral flow (fluorescent) vs. areas with low or no flow (nonfluorescent). Ten to fifteen seconds after TS injection, hearts were excised, cooled in isotonic KCl, opened and photographed. Several transmural longitudinal slices were cut from the posterior papillary muscle (PP). These were photographed under white light to record grossly necrotic areas and under ultraviolet light to record the gross distribution of fluorescence. The ultraviolet light source was a high intensity mercury Leitz lamp with a Zeiss BG 12 excitation filter and a Y2 yellow filter was used on the camera to exclude reflected blue and ultraviolet light. The transmural papillary muscle slices were fixed in 10% phosphate buffered formalin and histologic sections were prepared from each slice and stained with hematoxylin and eosin (H&E), by the periodic acid Schiff reaction (PAS) and with Hidenhain's variant of Mallory's connective tissue stain (CT). Necrosis was quantitated as percent of PP (transmural) by projecting histologic sections of the transmural PP slices onto heavy weight paper, tracing necrotic and spared areas, and cutting and weighing the respective areas of paper. Percent TS nonfluorescence was similarly calculated from the color slides. The groups were compared using the Student's nonpaired *t*-test.

### Results

Sixty-nine dogs were used. Sixteen of 33 (48%) untreated controls, 10 of 21 (48%) propranolol pretreated dogs and 10 of 15 (67%) propranolol delayed treated dogs survived the 24 hour period required for analysis of infarct size. Twenty-four dogs that died spontaneously developed ventricular fibrillation, usually during the first few minutes after occlusion. An additional 13 dogs died relatively late after the acute experiment, presumably from arrhythmias, although the ECG was not monitored. The number of dogs lost from each group was similar and occurred in an apparently random fashion. We could demonstrate no differences between dogs that lived and those that died when we assessed pre- or post-occlusion heart rate or blood pressure, lead II ST-segment elevation, or exact site of coronary occlusion.

All dogs that survived coronary ligation showed necrosis involving the posterior papillary muscle and surrounding myocardium. The lateral extent of infarction varied from dog to dog depending on coronary anatomy. The transmural extent of necrosis was more consistent within each group,

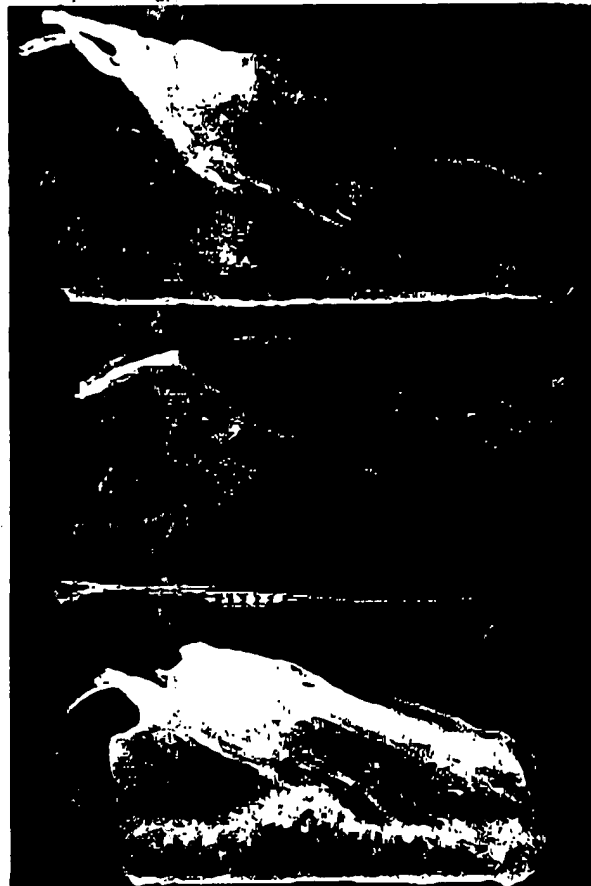


FIGURE 1. Transmural slices through the ischemic posterior papillary muscles of hearts from representative dogs of each group. All slices are photographed with endocardial surface up and chordae tendineae to the left. a) The top slice is from an untreated dog sacrificed after a 24 hour ligation of the circumflex artery. Necrosis is nearly transmural and consists of a central subendocardial zone (light area) of coagulation necrosis, a hyperemic (dark) midzone and a peripheral zone of necrosis and acute inflammation (light zone). A thin rim of subepicardial muscle (dark) is still viable. b) The middle slice is from a dog pretreated and continuously infused with propranolol and sacrificed after 24 hours of circumflex artery ligation. Necrosis (light areas), with scattered areas of hemorrhage, is present throughout the subendocardial and midmyocardial myocardium. The subepicardial third of the ischemic wall (dark zone) is viable. c) The lower slice is from a dog in which propranolol therapy was delayed until three hours after circumflex coronary ligation. Necrosis involves about three fourths of the transmural thickness and consists of a central core of coagulation necrosis (light), a hyperemic midzone (dark) and a peripheral zone of coagulation necrosis and acute inflammation (light). The subepicardial zone of viable muscle (dark) is intermediate between (a) and (b) in thickness.

permitting detection of significant differences between treatment groups. Slices through a representative heart from each group is shown in figure 1.

Necrosis was significantly reduced from  $85 \pm 4\%$  to  $52 \pm 4\%$  of the transmural posterior papillary muscle sections by continuous treatment with propranolol (table 1, fig.

TABLE 1. Parameters of Ischemic Injury and Collateral Flow in Dogs Surviving 24 Hours Coronary Ligation

Dog #	Max ST Elevation (mV)	Mean PCF (mm Hg)	% Non-fluorescence	% Necrosis
<b>Untreated</b>				
1774	0.9	—	92	96
1781	0.5	—	71	91
1927	0.4	—	52	71
1870	1.0	—	—	82
1880	0.6	—	—	72
1885	0.1	28	—	87
1889	0.4	23	—	78
1909	1.0	11	—	83
1918	1.0	28	77	72
1937	0.1	—	90	92
1938	0.2	—	—	92
1954	0.9	—	84	98
1959	0.6	28	56	71
2070	0.0	33	94	83
2077	0.3	30	62	93
2116	0.7	8	77	99
Mean ± SE	0.5 ± 0.1	23 ± 3	76 ± 5	85 ± 2
<b>Propranolol Pre-Rx</b>				
1877	0.1	30	17	52
1881	0.1	—	82	47
1890	0.4	18	44	55
1896	0.0	17	34	43
1906	0.1	23	41	40
1934	0.5	—	—	60
1943	0.0	10	73	32
1950	0.1	21	39	50
1955	0.1	28	49	33
1956	0.3	18	59	59
Mean ± SE	0.18 ± 0.06**	21 ± 2	43 ± 5	52 ± 4**
<b>Propranolol 8 Hr. Delayed Rx</b>				
2061	0.1	—	—	62
2067	1.0	18	89	85
2069	0.2	33	52	73
2072	0.5	16	75	72
2076	0.4	16	76	74
2085	0.5	18	54	69
2086	1.1	18	60	76
2094	0.2	15	44	48
2104	0.6	—	66	73
2107	0.8	18	65	79
Mean ± SE	0.5 ± 0.1	19 ± 2	62 ± 4*	71 ± 3**

\*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001 for treated vs. untreated groups compared with the Student's nonpaired *t*-test.  
 Abbreviations: Max ST elevation = maximum ST segment elevation in lead II of the standard ECG; PCF = peripheral coronary pressure.  
 Necrosis is expressed as a percentage of transmural sections through the posterior papillary muscle (see methods).  
 SE = standard error of the mean.

2). Delayed therapy with propranolol started three hours after occlusion resulted in  $71 \pm 3\%$  necrosis.

The maximum ST-segment elevation in lead II, which usually developed by five minutes after coronary occlusion, also was significantly less in dogs pretreated with propranolol (0.17 mV compared to 0.5 mV in both the untreated and delayed treatment groups) (table 1). Limb lead ST-segment elevation did not accurately reflect subsequent infarct size, however. The linear correlation coefficient for ST elevation (in untreated and propranolol pretreated dogs) vs. ultimate infarct size at 24 hours was only 0.47.

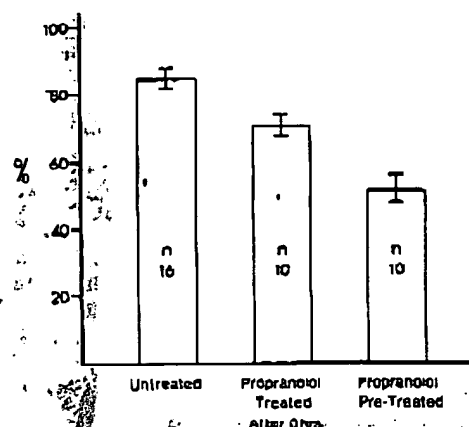


FIGURE 2. Transmural necrosis, calculated as described in the text, is compared in the three treatment groups. Brackets indicate the SEM. Pretreatment and continuous treatment with propranolol during coronary occlusion significantly reduced the transmural extent of necrosis ( $P < 0.001$ ). Delayed treatment also reduced necrosis ( $P < 0.01$ ) but was less effective than pretreatment.

The reduction in myofiber necrosis in propranolol treated dogs was apparently paralleled by smaller areas of microvascular injury. Pale zones of subendocardial myocardium and a surrounding zone of intramural hemorrhage, indicative of vascular damage,<sup>1</sup> were characteristically present in all three groups of dogs (fig. 1). Vascular damage within such areas is supported by the fact that myocardium within these areas was not perfused or stained (was non-fluorescent) after i.v. injection of thioflavin S. However, the amount of nonfluorescent myocardium in the posterior papillary muscle slices was reduced from  $76 \pm 5\%$  (untreated) to  $43 \pm 5\%$  by continuous propranolol treatment. The delayed treatment group showed  $62 \pm 4\%$  non-fluorescence (fig. 3).

Propranolol administration was usually associated with minor reductions in heart rate and mean arterial pressure. However, these parameters varied considerably between dogs, and within each dog over the 24 hr period of study, and no difference between groups was observed (table 2). Most dogs developed frequent ectopic beats and often showed continuous or intermittent runs of ventricular tachycardia. Ectopic activity was biphasic, being prominent in the first half hour, subsiding during the next 2-3 hours and then reappearing and continuing until sacrifice. The heart rate and the percent of total depolarizations which were ectopic on the ECG (in the awake state) 18 hours after occlusion (table 2) were not altered by propranolol treatment.

### Discussion

The results obtained from this study demonstrate that propranolol given prior to and continuously during coronary ligation markedly reduces the transmural extent of myocardial infarction. Previous studies have demonstrated that propranolol reduces epicardial ST-segment elevation<sup>2, 10</sup> and delays cell death in areas of severe ischemia so that smaller areas of necrosis occur subsequent to temporary coronary occlusion.<sup>11-13</sup> The present study demonstrates, by direct histologic quantitation, that moderately ischemic cells on

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FIGURE 3. Transmural slices through the ischemic posterior papillary muscles of hearts from representative dogs of each group. Each slice was photographed, endocardial surface up, under ultraviolet light after I.V. thioflavin S injection to demonstrate areas of persistent collateral flow (fluorescent, lighter areas) vs. areas with no thioflavin S penetrance (dark areas) and therefore insignificant collateral flow. a) The top slice from an untreated dog shows nearly transmural nonfluorescence. b) The middle slice is from a dog which was pretreated and continuously infused with propranolol. The papillary muscle itself is dark indicating insignificant microvascular perfusion but the outer two thirds of the section has been perfused by thioflavin S indicating microvascular preservation. c) The lower slice from a dog with delayed propranolol treatment demonstrates thioflavin S perfusion and therefore microvascular preservation in the subepicardial half of the section (light area).

the subepicardial wavefront of a developing myocardial infarct can be salvaged for at least 24 hours with continuous propranolol therapy. It seems likely that these cells could be salvaged indefinitely since coronary collateral blood flow gradually improves after one to four days of occlusion.<sup>14</sup>

The principal limitation to this type of study is the inability to evaluate necrosis in those dogs that die acutely following coronary occlusion. That this limitation did not

alter the conclusions of this study is supported by the facts that 1) mortality was similar in all three groups and 2) deaths were apparently random and could not be predicted from hemodynamic parameters, exact site of coronary occlusion, or magnitude of limb lead ST-segment elevation. The validity of using necrosis in transmural sections through the posterior papillary muscle as an index of infarct size has been shown previously.<sup>1</sup>

The potential for salvage of ischemic myocardium by therapy which is started subsequent to coronary occlusion (the situation which usually would apply in man) depends most importantly on the amount of ischemic but still viable myocardium available at the time therapy is begun. We previously have quantitated transmural necrosis with respect to duration of circumflex coronary occlusion in the dog. Irreversible cell injury in this model develops first in the subendocardial myocardium.<sup>16</sup> A wavefront of cell death then moves from the subendocardial zone of severe ischemia toward the subepicardial zone of more moderate ischemia.<sup>1,2</sup> By 40 min, about a third of the muscle in transmural sections through the posterior papillary muscle is already dead and becomes necrotic even if reperfusion is allowed. By three hours, an average of 57% of the transmural PP is dead<sup>1</sup> and by 24–96 hours, 85%. Thus, in dogs with circumflex coronary occlusions, there is ischemic myocardium which still is viable at three hours but which, in the absence of therapeutic intervention, dies by 24 hours. This salvageable myocardium includes at three hours  $(85-57)/85 \times 100$  or 33% of the 24 hour infarct. Propranolol therapy begun three hours after circumflex ligation salvaged only  $(85-71)/85 \times 100$  or 16% of the transmural infarct. However this 16% was about half of the average amount of ischemic muscle estimated to still have been viable and potentially salvageable when therapy was started.

The mechanism by which propranolol reduced the extent of myocardial necrosis is unknown. Dose response studies<sup>15</sup> have indicated that protection is related to  $\beta$ -blockade but have demonstrated maximum effect with the high dose used in the current study. d-propranolol, which shares with d-l-propranolol some direct cardiac depressant effects, is not a  $\beta$  blocker and does not reduce necrosis following temporary ischemic injury.<sup>15</sup>

$\beta$ -blockade in the anesthetized dog usually reduces heart rate and cardiac contractility and thereby decreases myocardial oxygen demands. Indices of contractility were not obtained in this experiment but heart rate and blood pressure were not significantly different in treated vs. untreated groups.  $\beta$ -blockade has a number of metabolic effects which may be important in delaying cardiac cell injury. These include inhibition of cardiac glycogenolysis and lipolysis<sup>16,17</sup> and inhibition of  $Ca^{++}$  accumulation by sarcoplasmic reticulum.<sup>18</sup> The role of each of these actions in preserving ischemic myocardium is unknown, however.

TABLE 2. Hemodynamic Data

Group	0-20 min postoccl		18 Hr postoccl	
	HR	MAP	HR	% Ectopic
A) Untreated	135 $\pm$ 23	112 $\pm$ 28	194 $\pm$ 34	60 $\pm$ 37
B) Propranolol Pre-Rx	132 $\pm$ 15	101 $\pm$ 21	170 $\pm$ 12	70 $\pm$ 10
C) Propranolol 3 Hr. Delayed Rx	150 $\pm$ 43	116 $\pm$ 24	176 $\pm$ 34	77 $\pm$ 13

Abbreviations: HR = heart rate; MAP = mean arterial pressure in mm Hg; % Ectopic = percentage of total beats per minute which were ectopic in the ECG sample taken at 18 hours.

Propranolol reduces total cardiac blood flow and reduces collateral blood flow within subendocardial, as well as subepicardial, layers of the ischemic myocardium.<sup>19</sup> Subendocardial flow, relative to subepicardial flow, may be unchanged or slightly improved.<sup>19, 20</sup> Collateral blood flow was not directly measured in the present study but peripheral coronary pressure, which has been used as an estimate of potential collateral flow,<sup>14</sup> was similar in treated and untreated dogs. It seems most likely that preservation of ischemic myocardium by propranolol was not related to improved oxygen delivery.

Although muscle cell death precedes microvascular injury in this model, microvascular necrosis eventually does occur and is associated with interstitial hemorrhage and subendocardial perfusion defects.<sup>1, 21</sup> Any therapeutic intervention which significantly reduces infarct size presumably must prevent necrosis of both cardiac muscle and the vasculature. Results with the dye thioflavin S suggest that propranolol did limit microvascular injury, as well as muscle necrosis. This conclusion is supported by ultrastructural analysis and by carbon black labelling studies.<sup>22</sup>

#### Conclusions and Clinical Implications

This study demonstrates that intervention with propranolol, in dogs with circumflex coronary occlusions, limits infarct size by preventing necrosis of moderately ischemic, subepicardial myocardium peripheral to the central core of the infarct. Although maximum benefit was achieved by initiating propranolol therapy prior to occlusion, some protection occurred when therapy was delayed for three hours. Initial results with low doses of propranolol during uncomplicated myocardial infarction in man have suggested that it reduces ST-segment elevation<sup>8</sup> and improves myocardial metabolism without precipitating congestive heart failure.<sup>9, 23, 24</sup> Propranolol also may prevent clinical infarct extension.<sup>25</sup> However, additional clinical trials will be needed to establish the potential benefits and risks of treatment with propranolol during acute myocardial infarction in man.

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